# EXHIBIT 1

Environomix
Environmental Medicine and Epidemiologic Consultants
110 Hickory Tavern Road
Meyersville, New Jersey 07933
Phone: 908-626-9515
Fax: 908-626-9517

# Methyl Tertiary Butyl Ether and Human Health Effects

**Expert Report in the Matter Concerning:**
**City of New York v.**
**Amerada Hess Corp., et al.**

**Prepared by**

**Sandra N. Mohr, MD, MPH**

**March 9, 2009**

Sandra N. Mohr, M.D. M.P.H. 3/09/09

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## SUMMARY OF CONCLUSIONS DRAWN IN THE TEXT

1. MTBE has been in use in gasoline for over 30 years as a replacement for lead in leaded gasoline, which has resulted in enormous public health benefits.

2. MTBE has received FDA approval for use as a human medication to dissolve gallstones. This has been used for over 20 years with no long-term toxic injuries reported.

3. Human studies using experimental exposures to MTBE have failed to demonstrate any impairments in neurobehavioral or physiologic measurements in the participants at air levels found in the environment (gasoline refueling and gas station maintenance and pump repair). This includes among those participants who were self-described as "sensitive" to MTBE.

4. MTBE has been used in gasoline for 30 years with no published reports from state sponsored tumor registries or the U. S. National Death Index of increased cancers linked to MTBE exposures.

5. The USEPA has recommended an organoleptic standard for MTBE at 20-40 ug/L; a level at which there is little likelihood of any adverse human health effects. The New York MCL for MTBE is set at 10 ug/L, which is even more protective.

6. MTBE has never been classified as a human carcinogen by the U.S. Environmental Protection Agency or the International Agency for Research on Cancer.

All conclusions here and in the body of the text of this report are based on a reasonable degree of scientific and medical certainty. I reserve the right to supplement by expert report as additional information becomes available and is provided to me.

## EXPOSURES TO MTBE AND THE DEVELOPMENT OF HUMAN ILLNESS

### GASOLINE AND METHYL TERTIARY-BUTYL ETHER

Gasoline is a refined petroleum product that is used as a motor fuel. Gasoline is a mixture and may contain over 250 hydrocarbons as well as small quantities of additives and blending agents. The exact composition of gasoline varies with the production location of the crude oil, which is then refined, and what fractions are blended and which additives are instilled for various climates, locations and seasons. The analysis of one finished motor fuel resulted in these hydrocarbons being identified: n-paraffins 11.45%, branched paraffins 46.55%, cycloparaffins 4.68%, olefins 8.96% and aromatics 28.36% (including benzene 1.69%, toluene 3.99%, ethylbenzene 1.69% and xylenes 8.14%) (King 1988). More recent changes in gasoline refining and blending have led to the average amounts of benzene in gasoline to fall to $\leq 1\%$.

Gasoline exposure to the public occurs primarily through the inhalation of the vapor during automobile refueling. Of the more than 300 million gallons of gasoline that are consumed each year in the United States, the U.S. Environmental Protection Agency estimated that about 4 million gallons were emitted into the ambient air in 1982. About 40% of the vaporization occurs at service stations. A self-service gasoline customer would typically experience approximately 200 parts per million (ppm) of gasoline hydrocarbons over a period of about 2 minutes while pumping the gasoline (ATSDR 1993). One additive blended into gasoline has been MTBE.

Methyl tertiary-butyl ether (MTBE) is a chemical, which was added as an octane enhancer and anti-knock agent to gasoline after the phase-out of lead containing fuels in the 1970s. At that time, MTBE was added to fuels as an octane booster in concentrations of less than 1% (by volume) to regular gasoline and from 2% to 9% in premium gasoline in the 1970s. The replacement of lead in gasoline has resulted in enormous public health benefits. Lead is a neurotoxin affecting the brains of developing children; higher doses can lead to effects in other organ systems. The New York State Department of Health requires all children to be testing for blood lead levels at the ages of 1 and again at 2 years. Blood lead levels greater than 10 ug/dl are considered high for children and must be appropriately investigated and treated (New York State DOH 2009). The removal of lead from gasoline has had dramatic affects on children's lead levels. According to data from the second National Health and Nutrition Examination Surveys (NHANES) from 1976-1980 and phase I of the third National Health and Nutrition Examination Survey (NHANES) from 1988-1991, the mean blood lead level of children aged 1 to 5 years declined 77% (13.7 to 3.2 ug/dl) in non-Hispanic white children and 72% (20.2 to 5.6 ug/dl) in non-Hispanic black children. These findings lead the researchers to state, "The major cause of the observed decline in blood lead levels is most likely the removal of 99.8% of lead from gasoline and the removal of lead from soldered cans" (Pirkle 1994). Using the same decreases in blood lead levels from the NHANES surveys, researchers using data from published meta-analysis estimated a reduction of 0.185 to 0.323 IQ points for each 1g/dl blood lead concentration. These data estimated that children in the late 1990s had IQs that were on average 2.2-2.7 points higher than preschoolers of the same age in the 1970s.They estimated that each IQ

point raises a worker's productivity 1.76-2.38%. With discounted lifetime earnings of $723,300 for each 2-year-old in 2000 dollars, the estimated economic benefit for each year's cohort of 3.8 million 2-year-olds ranged from $110-$319 billion (Grosse 2002).

In 1992 the use of MTBE in fuels was expanded from being a replacement for tetraethyl lead to that of an anti-pollutant. MTBE was added to wintertime, oxygenated fuels at up to 2.7% oxygen by weight (15% volume of MTBE) to decrease tailpipe carbon monoxide emissions in areas of nonattainment of the National Ambient Air Quality Standards established under the Clean Air Act Amendments of 1990 (NRC 1996). MTBE was chosen as a major oxygenate for wintertime oxygenated fuel [over Ethyl Tertiary Butyl Ether (ETBE) and Tertiary Amyl Methyl Ether (TAME)] mostly because of its cost and performance characteristics (high octane number, low sulfur content, blending vapor pressure and boiling point) (Ahmed 2001) but also because of its safety in more than 20 years of use in American gasoline formulations and its use in clinical medicine.

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## HUMAN MTBE CLINICAL STUDIES

In Europe, pharmaceutical grade MTBE (>99% pure) (Leuschner 1991) has been used in the treatment of gallstones. Data from over 800 patients treated at 21 European hospitals with MTBE for gallstone dissolution are available. These patients underwent percutaneous transhepatic puncture of the gallbladder and infusion of MTBE. All side effects were transient. Two hundred and sixty-four of the patients were followed for 5 or more years. No long-term toxic injuries from the ether were reported (Hellstern 1998, Leuschner 1991,1994).

In the United States, MTBE has been approved by the Federal Food and Drug Administration for investigational status for use in intraductal injection to dissolve cholesterol gallstones. In a study of 75 patients treated with MTBE instilled into the gallbladder through a percutaneous transhepatic catheter, 23 patients experienced transient nausea with or without vomiting. When MTBE overflowed the gallbladder and systemic absorption occurred, transient sedation was also reported (Thistle et al, 1989). In a similar case series of 24 patients done in Germany, 16 patients had abdominal pain; two patients exhibited a slight increase in leukocytes, two patients a slight increase in bilirubin and nine patients showed an slight increase in transaminases within five days after puncturing the gallbladder and MTBE application (Holl et al, 1991). In Great Britain, 33 patients were treated with MTBE through a nasobiliary catheter; 13 patients experienced drowsiness, 8 an elevation of liver enzymes, 5 experienced pain on infusion of MTBE, 6 nausea, 5 anorexia, 2 hypotension, and 1 each for headache, palpitations and angina (Neoptolemos et al 1990). The Italian experience upon which the subsequent trials were based reported a case series of three patients with nausea and somnolence as the major adverse effects of MTBE administration (DiPadova et al, 1986). MTBE continues to be an effective alternative to surgery in high-risk patients with acute cholecystitis due to gallstones (Mulagha 1999.)

such as exposing volunteers to drinking MTBE in water or breathing in MTBE either as a pure subject or mixed in gasoline all thought to be reasonably safe by their respective review committees.

**DRINKING WATER**

In order to prevent or reduce the chances of health effects from occurring due to drinking contaminated water, "Maximum Contaminant Levels" (MCLs) have been established by the USEPA. MCLs are set at levels well below those known to cause health effects in lab animals and workers. States may choose to set MCLs lower than federal requirements. The U.S. Environmental Protection Agency (USEPA) has not promulgated a MCL for MTBE due to the "many uncertainties and limitations associated with the toxicity data base for this chemical" (EPA 1997).

The USEPA has issued guidelines in an "Advisory" based on organoleptic (odor and taste) properties. In this Advisory, the EPA uses a risk characterization method called 'Margin of Exposure (or safety)' that is "how far the environmental exposure of interest is from the lower end of the exposures at which animals or humans have shown some toxicity effect." After reviewing taste and odor publications, the EPA noted that while the organoleptic characteristics could not be used to develop primary drinking water standards or MCL, a recommended range of 20-40 ug/L (20-40 ppb) would help ensure consumer acceptance. They note that at 20 ug/l, the "Margin of Exposure" (or safety from exposure) is approximately 40 thousand for cancer effects (seen in animals at high doses) and over a hundred thousand for some noncancer effects. They note that at 4 to 5 levels of magnitude of protection, there was little likelihood that drinking water with concentrations of MTBE of 20-40 ug/L would cause adverse effects in humans although some people might be able to detect the odor or taste below that level (EPA 1997).

The New York MCLs for drinking water include 10 ug/L (10 ppb) for MTBE, which should assure an even greater margin of safety and consumer acceptance of their drinking water.

***The USEPA has recommended an organoleptic guideline for MTBE at 20-40 ug/L; a level at which there is little likelihood of any adverse human health effects. The New York MCL for MTBE is set at 10 ug/L, which is even more protective.***

**CARCINOGENICITY OF MTBE**

According to a Rand Corporation monograph, 31 states have tumor registries in the United States (Rand Corporation). All patients diagnosed with cancer in these states are required by law to have the tumor type reported to the state. Generally these registries also contain the names, addresses and often occupations of the diagnosed patients. Some registries may contain additional information such as cigarette smoking histories or whether tissues from the tumor biopsy are banked for research purposes. Epidemiologists employed by the state Departments of Health are required to review these databases looking for cancer clusters around environmental sites or occupation. Additionally, since

the databases are generally considered public records, states often form partnerships with university researchers to look for trends and clusters. Despite MTBE being in use for 30 years in gasoline, none have reported any cancer clusters around MTBE spill sites, nor clustering around manufacturing sites, nor with specified highly exposed occupations.

The United States maintains a database known as the National Death Index (NDI). This database captures death certificate data for all persons who have died in the United States. These data include the name, address, date of birth, date of death and occupation of the deceased. This database is available to all researchers (generally, but not limited to professors of epidemiology at universities) who look for trends in causes of death (including due to cancer) in the United States. No papers have been published from NDI data linking increased cancers to MTBE contaminated areas/addresses or MTBE exposed occupations.

***MTBE has been used in gasoline for 30 years with no published reports from state sponsored tumor registries or the U. S. National Death Index of increased cancers linked to MTBE exposures.***

The International Agency for Research on Cancer (IARC) has reviewed the human and animal toxicological data on MTBE. The IARC has listed MTBE as having limited evidence for carcinogenicity in experimental animals and inadequate evidence in humans. IARC lists MTBE as not classifiable as to its carcinogenicity to humans (group 3) (IARC). Likewise, The USEPA has reviewed the same human and animal data but has not issued a formal carcinogenicity ranking for MTBE. USEPA documents do find that MTBE may be carcinogenic in animals at high doses sometimes at exposure levels that have exceeded the maximum tolerated dose. When setting the secondary drinking water guidelines at 20-40 ug/l of MTBE, the USEPA noted that "the margins of exposure [safety] are about 10 to 100 times greater than would be provided by an EPA reference dose (RfD) for noncancer effects," and further that "they are in the range of margins of exposure [safety] typically provided by National Primary Drinking Water Standards under the Federal Safe Drinking Water Act to protect people from potential carcinogenic effects" even though the USEPA has never listed MTBE as a human carcinogen. The National Toxicology Program has stated that MTBE is an animal carcinogen, but did not list it as being anticipated to be a human carcinogen (NTP 1999). The most recent evaluation for carcinogenicity was in the European Union's Risk Assessment Report. The EU has classified undiluted MTBE as a skin irritant and highly flammable, but not as a carcinogen or any other hazard, which would require labeling in the EU (MacGregor 2006).

***MTBE has never been classified as a human carcinogen by the U.S. Environmental Protection Agency or the International Agency for Research on Cancer.***

Two recent reviews in the peer reviewed published scientific literature come to similar conclusions, that for the majority of the non-occupationally exposed population, MTBE is unlikely to produce lasting adverse health effects (Ahmed 2001) and that evidence for carcinogenicity is unconvincing (McGregor 2006).

**COMMENTARY ON PLAINTIFFS' EXPERT REPORT**

I have read the report by Dr. Kathleen Burns. Please note that on page ten of her report, Dr. Burns states that she "adapted summary tables" from the "Toxicological Profile of [sic] MTBE" by the CDC. In actuality, the ATSDR "Toxicological Profile for MTBE" contains no such table. It does contain table 2.1 on page 11 of that document which does list the two human inhalation studies by Prah and Cain summarized earlier in this report. Not only does the ATSDR table not list "eye irritation" as a consequence of the MTBE exposure in these two studies, the studies themselves do not report any eye irritation or changes in tear film breakup time. (Similarly there were no ocular symptoms from exposure to more than 20 times this level in humans in the Nihlen study.)

Additionally, the ATSDR Table 2.1 on page 11 lists the levels from those two studies of 1.7 ppm (1700 ppb) and 1.39 ppm (1390 ppb) as "No Observable Adverse Effect Levels" in humans. This is contrary to Dr. Burns assertion on page 5 of her report that there is "no credible or proven 'safe' level of MTBE exposure" and she leaves out this part of the ATSDR table in her own "adapted" one. She also includes a row in her "adapted" table regarding gallbladder treatment and does acknowledge that this row is not in the ATSDR report. In the row she lists numerous treatment effects, but does not provide any references for her health effects assertions. As a nonclinician, it is unclear whether Dr. Burns has the expertise to discern the difference between liver abnormalities due to the gallstones and those due to the treatment. The actual experience with using MTBE as a treatment is summarized and the actual references cited on page 7 of this report.

On page 13 of Dr. Burn's report she states that, "it is impossible to predict how individuals will respond at specific exposure levels." This statement is contrary to the science of toxicology. The concept of specific exposure level, or dose, is a basic tenet in science and well recognized by society. We do not expect the same behavior (toxicity) from a person who drinks an 8 ounce glass of an alcoholic beverage as we do from one who drinks one drop of alcohol in an 8 ounce glass of water, nor do we assign as a society the same consequences to those behaviors. It is well recognized that acetaminophen (sold as Tylenol and other brands) causes liver failure and death in humans, but not at the doses recommended for fever and pain relief. As a society we can and do regulate chemicals at levels that we believe are safe for even the most sensitive members of the population.

Dr. Burns relies solely on mutagenicity assays and animal studies and fails to review the published human literature on MTBE exposure. Furthermore, she is very selective of which mutagenicity studies she chooses to rely upon. According to the USEPA, which reviewed all available mutagenicity studies at the time, "with one exception, this chemical [MTBE] has not exhibited genetic toxicity in a variety of in vitro and in vivo mammalian and non-mammalian test systems." The single exception was a mouse lymphoma assay which was thought to be positive due to *in vitro* and not *in vivo* metabolism and therefore of limited importance. The USEPA summarized that the weight of evidence "indicated that MTBE is not mutagenic" (EPA 1997). The USEPA document was "peer reviewed both internally in the Agency and externally by experts in the field

before its release to the public" (EPA 1997). More recently, twenty-five genotoxicity assays were reviewed with the author finding, "The data indicative of genotoxicity are very weak, with none of the studies indicating significant activity having been independently verified, except for the mutagenicity in mouse lymphoma cells" (McGregor 2006). Dr. Burns relies upon Du et al. citing that MTBE causes DNA adducts. However, this study has been criticized in that the way it was conducted, it was impossible for the authors to know whether the tagged carbon on the DNA came from a DNA adduct or from the metabolism of MTBE to formaldehyde and from the 1-carbon pool into normal incorporation into DNA (Swenberg 2008).

Dr. Burns condemns "industry" for misinterpreting studies looking at MTBE exposures and developmental outcomes and stating these studies were referred to as "showing that MTBE did not cause any particular hazards to pregnant women or children" (page 25). This statement is misleading, because in reality none of these studies deal with pregnant women or children at all as they are all animal studies. Like tumor registries, many states have birth defects registries. The New York State Congenital Malformations Registry is one of 34, which submits data to the National Birth Defects Prevention Network. The data in the registry undergoes consistent surveillance for changes in rates and trends (New York State Department of Health 2004). Despite MTBE being in use for 30 years in gasoline, there have been no reported birth defects clusters around MTBE spill sites, nor have there been any reported clusters around manufacturing sites.

Dr. Burns opines that MTBE is a carcinogen. This statement is very misleading as there is no reliable scientific basis to conclude that MTBE or its metabolites may be carcinogenic based on the levels of MTBE to which humans may be exposed in drinking water. She fails to acknowledge that other panels of reputable (and non "industry" scientists) have reviewed the same data as she has and neither the National Toxicology Program at the National Institutes of Health, IARC nor the EU, have voted to list MTBE as a human carcinogen. She notes that MTBE metabolites, TBA and formaldehyde, are also carcinogenic. TBA, used in the manufacture of perfumes, has been studied in some animal assays but is not classified as a human carcinogen under USEPA. While high doses of formaldehyde are carcinogenic, a small amount of formaldehyde formation is a normal part of the metabolism of foods in the human body and is essential in de novo purine synthesis and amino acid synthesis (nucleic acid and protein manufacture) as noted by Dr. Swenberg.

Dr. Burns opines that MCL levels for MTBE in water vary from state to state but does not address the difference between a MCL for protecting health and a guideline that is set even lower for organoleptic reasons. The USEPA did originally propose to issue an MCL for MTBE at 70 ug/L as a health-based standard. However, because of taste and odor studies, some conducted in California, it became clear that this standard, while protective for health, did not address issues of water taste and odor. USEPA has not issued a primary MCL to date, and instead has issued secondary guidelines based on organoleptic (odor and taste) properties at a range of 20-40 ug/L (20-40 ppb) that would help ensure consumer acceptance and were even more protective. They note that at 20 ug/L, the margin of exposure (or safety) is approximately 40 thousand times less than the range of cancer effects seen in animals at high doses and would be twice that (80

thousand times less) by drinking a concentration of half the amount such as the New York State MCL of 10 ug/L. Furthermore, this margin of exposure is 10 to 100 times more protective than that which would be set under a primary drinking water standard for noncancer endpoints such as birth defects (EPA 1997).

**SUMMARY**

Petroleum products, such as gasoline, are complex mixtures of aliphatic and aromatic hydrocarbons as well as additives, such as MTBE. Gasoline is a ubiquitous substance found not only at service stations and in automobile fuel tanks, but also in many homes in order to fuel lawn mowers, leaf and snow blowers, motorboats and other power motors. The general public has exposure to small amounts of the constituents of gasoline everyday from evaporative emissions from service stations and automobiles, as well as from home use. The components of gasoline are not unique to that substance, many other uses for individual constituents have been found in the occupational setting and in products used in the home.

People are exposed to cancer causing agents every day of their lives. Some foods, medications and even sunlight can cause cancer. The vast majority of the chemicals in gasoline are not carcinogenic. There is no scientific evidence that MTBE causes cancer in humans. There is limited evidence that MTBE does cause cancer in mice and rats at very high doses. Some of these cancers, such as kidney cancers in male rats may not be relevant to human health, because male rats have a protein, which is not found in humans, which causes them to develop kidney cancers due to exposure to any branch chain hydrocarbons (e.g. rubbing alcohol), which are not carcinogenic in humans.

The inhalation of gasoline and its constituents at high enough doses does cause acute health effects, which are short in duration and self-limited with the cessation of exposure. These effects are due to the irritative and anesthetic properties of the chemicals. The no-observable-adverse-effect-level (NOAEL) is that level of a chemical at which people can be exposed and have no ill effects. Exposures to gasoline vapors at up to 160 ppm cause only eye irritation, but no central nervous effects. Exposures to MTBE at up to 50 ppm may cause a slight swelling in the nasal-sinus passages with a slight decrease in the ability to blow forcefully through the nose, but no central nervous system effects (headache, drowsiness, incoordination). This would indicate that the NOAEL for gasoline is at or near the 150 ppm level and 50 ppm for MTBE. There are no studies in the peer reviewed scientific literature to demonstrate any aberrations of normal human physiology from exposure to MTBE at any levels lower than 50 ppm (50,000 ppb).